1.04-5.58, p = 0.04) when compared with UCB, but not with BM as cell source (p = 0.17).

This retrospective single institutional study of 628 consecutive allogeneic transplantation patients revealed some novel findings. PSC were associated with a higher incidence of aGVHD, but not cGVHD. The combination of FK/MTX was associated with a lower risk of cGVHD than CSA/MTX and will need to be investigated further. Validation of these findings requires large cooperative prospective studies.

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TNFα -238A ALLELE IDENTIFIES PATIENTS WHO DEVELOP BOTH ACUTE AND CHRONIC GVHD AFTER MATCHED UNRELATED DONOR TRANSPLANT IN CHILDREN: A PEDIATRIC BLOOD AND MARROW TRANSPLANT CONSORTIUM STUDY

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Introduction: The inflammatory cytokine tumor necrosis factor-α (TNFα) plays a central role in the pathogenesis of acute GVHD, but its role in chronic GVHD is less clearly defined. We recently described an association between the recipient TNFα gene polymorphisms and the severity of acute GVHD in pediatric unrelated donor BMT (Goyal et al, *Biol Blood Marrow Transplant*, 2010). We now report the correlative analyses between the recipient and donor TNFα promoter region single nucleotide gene polymorphisms (SNP) and the risk of acute and chronic GVHD in this cohort.

Materials and Methods: Genotyping was performed on pretransplant genomic DNA samples from recipient-donor pairs (n = 180). To address the confounding effect of population stratification, significant associations were reanalyzed in white recipient-donor pairs.

Results: Twenty-three patients died before day+100; 78/153 (51%) of the remaining evaluable patients developed cGVHD with extensive disease in 60/76 (79%) patients. Similar to findings in recipients, the donor TNFα variant A allele of -863C/A SNP (HR 3.67, p = 0.01) and the variant C allele of -1031T/C SNP (HR 2.85, p = 0.05) were also associated with grade III-IV aGvHD. The recipient TNFα variant A allele of - 238G/A SNP was associated with grade II-IV aGVHD (HR 2.38; p<0.01, previously reported) as well with cGVHD (RR 1.68; P = 0.02). Six out of 44 (14%) patients (14%) with variant -238A allele compare to 40/99 (40%) patients without -238A allele did not develop acute or chronic GVHD. The rates of only acute (16%, 18%) and only chronic GVHD (18%, 19%) were similar in those with or without recipient -238A allele, respectively. However, 23/44 (52%) patients with the -238A allele developed both acute and chronic GVHD compared with 22/99 (22%) without the -238A allele (RR 2.35, p<0.01, Table 1). These associations remained significant when analyzed in white-only recipient-donor pairs. No statistically significant association was detected between the donor TNFα gene polymorphisms and the risk of cGVHD.

Table 1.

Recipient TNF alpha -238 G>A	No Acute or Chronic GVHD	Only Acute GVHD	Only Chronic GVHD	Both Acute & Chronic GVHD	P-Value
AA/AG	6/14 (14%)	7/44 (16%)	8/44 (18%)	23/44 (52%)	<0.01
GG	40/99 (40%)	18/99 (19%)	19/99 (19%)	22/99 (22%)	

Conclusions: In this large cohort of pediatric matched unrelated donor transplants: 1) The recipient and donor TNFα -863A allele and -1031C allele are associated with grade III-IV aGvHD. 2) The recipient TNFα -238A allele identifies a subset of patients who develop both acute and chronic GVHD. These findings deserve further study in independent cohorts and may be clinically relevant in a risk-adjusted approach to GVHD management in pediatric unrelated donor transplants.

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COMPARISON OF SIROLIMUS AND MYCOPHENOLATE MOFETIL AS SALVAGE TREATMENT FOR ACUTE GRAFT-VERSUS-HOST DISEASE

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Glucocorticoid refractory acute GVHD (aGVHD) is a major source of mortality following allogeneic HCT. Comparative studies to evaluate the efficacy of salvage immune suppressive agents are lacking. We retrospectively compared the efficacy of sirolimus (SIR) and mycophenolate mofetil (MMF) as salvage aGVHD therapy for glucocorticoid refractory, dependent or intolerant patients. Of 281 consecutive patients who received allogeneic HCT from 07/2004 to 09/2009, we identified 84 patients who received tacrolimus/methotrexate (Tac/MTX) GVHD prophylaxis, were treated with glucocorticoids for grades 2-4 aGVHD, were refractory (n = 72) or dependent (n = 12) to glucocorticoids, and received 2nd line GVHD treatment with MMF (n = 56) or SIR (n = 28). Demographics and treatment variables were similar except for year of transplant (earlier for MMF). Disease diagnoses included AML (n = 27), NHL (n = 14), MDS (n = 12), ALL (n = 9), CML (n = 7), CLL (n = 4), SAA (n = 2), MPD (n = 5), MM/PCL (n = 3), and HL (n = 1). Conditioning regimens were busulfan/fludarabine for 71, and other regimens for 13. Except for 1 bone marrow graft in each group, all received peripheral blood stem cells. Graft sources were from HLA-matched siblings (35), or 8/8 HLA-matched unrelated donors (49). Overall grade distribution of aGVHD at time of salvage for MMF vs. SIR was the following: grade 1 (13 vs. 2), grade 2 (31 vs. 16), grade 3 (9 vs. 5) and grade 4 (3 vs. 5). Median steroid dose at the time of salvage was 1 (range 0.17 – 2.28) mg/kg for MMF group and 1 (range 0.12 – 2.0) mg/kg for SIR group. Median time from steroid to salvage was 20 (range 1 – 208) days for MMF and 19 (range 1 – 275) days for SIR (p = 0.84). Complete response (CR) rates following initiation of MMF or SIR did not significantly differ at the following time points: 1 week (MMF 30%, SIR 21%), 4 weeks (MMF 44%, SIR 46%), and 6 weeks (MMF 60%, SIR 58%). Overall response rates (ORR) also did not differ significantly: 1 week (MMF 57%, SIR 42%), 4 weeks (MMF 57%, SIR 77%), and 6 weeks (MMF 72%, SIR 75%). Flare or progression of aGVHD while on salvage regimen was noted in 50% (MMF) and 36% (SIR) of patients (p = 0.64). Median overall survival from the time of salvage therapy for MMF vs. SIR did not significantly differ, 11.6 (95% CI 7.0 – 28.1) vs. 9.7 (95% CI 5.4 – 15.9) months, log-rank p = 0.88. These retrospective data suggest that MMF and SIR have comparable activity in the treatment of steroid refractory or dependent acute GVHD.

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HUMAN MULTIPOTENT ADULT PROGENITOR CELLS EFFECTIVELY MODULATE ALLOREACTIVITY AFTER BONE MARROW TRANSPLANTATION REDUCING GVHD WHILE PRESERVING GRAFT-VERSUS-LEUKEMIA ACTIVITY

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Graft-versus-host disease (GVHD) limits successful outcomes following allogeneic BMT (allo-BMT). The pathophysiology of GVHD involves three distinct phases which contribute to inflammatory cytokine dysregulation, the generation of cellular effectors, and target organ injury. This framework uncovers opportunities to regulate GVHD. We examined whether reported immunosuppressive and regenerative properties of human, bone marrow-derived multi-potent, adult progenitor cells (hMAPCs) could regulate GVHD using established murine models. The immuno-regulatory